Approval Process Overview and Oversight

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CBER REGULATORY AUTHORITY

- **BIOLOGICS**
- **DEVICES**
- **DRUGS**
- **HUMAN TISSUE INTENDED FOR TRANSPLANTATION**

CBER REGULATORY AUTHORITY

- **BIOLOGICS**
  - Investigational New Drug Exemptions (IND, 21 CFR 312)
  - Biologics License Applications (BLA, 21 CFR 600-680)
- **EXAMPLES**
  - Vaccines and allergenics
  - Blood Products (including blood grouping reagents and donor screening tests for bloodborne pathogens)
  - Therapeutics (monoclonal antibodies, cytokines, cellular & gene therapies, xenotransplantation)

CBER REGULATORY AUTHORITY

- **MEDICAL DEVICES**
  - Investigational Device Exemptions (IDE, 21 CFR 812)
  - Premarket Approval Applications (PMA, 21 CFR 814)
    - Product Development Protocol (PDP, 21 CFR 814.19)
    - Humanitarian Device Exemption (HDE, 21 CFR 814 Subpart H)
  - Premarket Notifications (510(k), 21 CFR 807 Subpart E)
- **EXAMPLES**
  - Blood Collecting and Processing Devices
  - Donor blood compatibility tests, bloodborne pathogen tests and associated testing instruments
  - Blood establishment computer software

CBER REGULATORY AUTHORITY

- **DRUGS**
  - Investigational New Drug Exemptions (IND, 21 CFR 312)
  - New Drug Applications (NDA, 21 CFR 314)
  - Abbreviated New Drug Applications (ANDA, 21 CFR 314 Subpart C)
- **EXAMPLES**
  - Blood Collection Bags (anticoagulants)
  - Thrombolytics (clot busters)
  - Blood preservatives

CBER REGULATORY AUTHORITY

- **HUMAN TISSUE INTENDED FOR TRANSPLANTATION**
  - **Human Tissue Intended for Transplantation (21 CFR 1270)**
- **EXAMPLES**
  - **Bone, Skin, Corneas, Ligaments, Tendons**

OVERVIEW OF THE APPROVAL PROCESS

- **CBER's PREDOMINANT APPROVAL PATHWAY IS THE IND/BLA**
  - Most submissions are IND/BLA related
  - Many principles of the IND/BLA pathway are found in the other approval pathways
- **OTHER PATHWAYS USE THE SPECIFIC PATHWAY REGULATIONS/GUIDANCE**
  - Device and drug reviews are conducted using device and drug regulations and guidances respectively

LICENSES

21 CFR 601.2

One License:

- Biologic License
  - Product & Establishment Licenses are now obsolete

21 CFR 601.2c

- Biologics License for Specified Products

PRESCRIPTION DRUG USER FEE ACT (PDUFA)

- **Performance goals**
  - Clinical Hold Responses
  - Review and Act On
- **Management goals**
  - Discipline Reviews
  - Two Level Resubmissions Class 1 and 2
  - Meeting Management

Managed Review Process

- **Developed to facilitate meeting PDUFA requirements**
- **Standardized the review process**
  - **Goal dates**
  - **Target dates**
- **Helped standardize review expectations**
  - **Content**
  - **Documentation**

IND PHASE

- **Pre-IND meeting**
  - **CBER SOPP 8101.1 Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants**
- **Identify potential review committee**
- **Consider Advisory Committee needs & schedule**
- **Arrange for BiMo Inspection**

THE REVIEW COMMITTEE

CONSTITUTED TO CONTAIN THE NECESSARY EXPERTISE TO REVIEW THE SUBMISSION

RESPONSIBILITIES

CHAIRPERSON/LEAD

- CONSTITUTE the committee
- ASSIGN sections for review
- SCHEDULE and CONDUCT meetings
- WRITE “action” letters
- PRESENT at Advisory Committee Meetings
- REQUEST a pre-license inspection
- PREPARE a Summary of Basis for Approval (SBA)

RESPONSIBILITIES

REGULATORY PROJECT MANAGER

- MANAGE the review of the application
- REVIEW assigned portions of application
- PERFORM quality control check on the review
- ASSURE reviews are documented properly
- ASSURE review of labeling is complete
- COORDINATE compliance status check
- PREPARE approval letter for new products
- PREPARE finding of no significant impact

RESPONSIBILITIES

DISCIPLINE REVIEWER

- REVIEW assigned sections of the application
- WRITE an annotated review memo
- ATTEND review committee meetings
- COMMUNICATE with the applicant as necessary and document the discussion
- PREPARE for Advisory Committee meetings
- PARTICIPATE in the pre-approval inspection (if necessary)
- CONSIDER if a public health and/or research questions need to be answered relative to product approval

WHO SUBMITS?

MANUFACTURER

- **Any legal person or entity who is engaged in manufacture**

or

- **An applicant for a license who takes responsibility for compliance with product and establishment standards**

WHAT DO THEY SUBMIT?

- **Biologics License Application (BLA)**
- **Supplements & Annual Reports**

BIOLOGICS LICENSE APPLICATION

Submitted on FDA 356h

- **Source material / raw materials**
- **Manufacturing information**
- **Pre-clinical studies**
- **Clinical studies**
- **Labeling**

BIOLOGICS LICENSE APPLICATION

Submitted on FDA 356h

- **Name, address & phone number of manufacturer**
- **Name & address of facilities**
- **Authorized official**
- **Facility information**
- **Utilities information**
- **Contamination/cross-contamination information**
- **Environmental assessment or categorical exclusion**

CBER

International Harmonization

- **Using the CTD**
  - An agreed upon common format for the modular presentation of summaries, reports and data
  - Content is harmonized to the extent of relevant ICH guidelines
  - 5 modules:
    1. Regional Specific Information
    2. Quality Overall Summary
    3. Quality
    4. Non-clinical Study Reports
    5. Clinical Study Reports

Electronic Submissions

- **Submission of BLA/S may be made on paper or electronically**
- **Submissions should be made in accordance with published guidance:**
  - **http://www.fda.gov/cber/esub/esub.htm**

APPLICATION RECEIVED

- **Administrative processing**
  - Submission tracking number assigned (STN)
  - data entry
  - user fee verification
- **First committee meeting**
  - review assignments
  - time frames

SUBMISSION TRACKING NUMBER
aaaaaa.bbbb/cccc

FILING REVIEW

- **Review for completeness**
  - **RTF policy**
  - **CBER SOPP 8404 Refusal to File Guidance for Product License Applications and Establishment License Applications**
- **Filing meeting**
- **Filing letter**
- **Notify applicant of any deficiencies identified during filing review**

REFUSE TO FILE

A refusal to file (RTF) letter is issued when the submission has been deemed not sufficiently complete for a meaningful review

21 CFR601.2(a), RTF Policy, SOPP 8404

COMPLETE REVIEW

- **Substantive review**
  - Information requests
  - Review memos
  - Discipline reviews
  - labeling
  - lot release protocols
- **Inspections**
  - Facility
  - Bioresearch Monitoring
- **Advisory Committee presentation**

REVIEW MEMO

- **Typed, Signed and Dated**
- **What was reviewed**
  - **Which application?**
  - **Which sections?**
- **Comments and questions**
  - **Annotated (page and line numbers)**
  - **Questions are prepared for incorporation into a Discipline Review or Complete Response letter**

INFORMATION REQUESTS (IRs)

- Issued while the review is in progress
- Requests information needed to continue the review
- IRs may be made by letter, telephone or FAX
- IRs are documented in the file
- The response to an information request should not be so great as to constitute a major amendment
- Responses to information requests do not necessarily have to be reviewed in the current review cycle
- DOES NOT STOP THE REVIEW CLOCK

DISCIPLINE REVIEWS (DRs)

- A DR letter is issued when a particular discipline (clinical, CMC, etc.) has finished its review, but the complete review is not yet done
- A DR letter contains comments and questions that might appear in the action letter
- Responses to DR letters need not necessarily be reviewed prior to issuance of the action letter
- DOES NOT STOP THE REVIEW CLOCK

ADMINISTRATIVE RECORD

Copies of Telecons, FAXes, Review Memos, Meeting Minutes, etc., become part of the administrative record and are entered into the file and the tracking system

C B
E R

ACTION DECISION

- **After a complete review is finished**
  - Inspections
  - Advisory Committee
- **Review Committee meeting**
  - Outstanding issues
  - Agreements & commitments
- **License action recommendation**
  - Not ready for approval
  - Approval

Scientific Dispute Resolution Within the Team (Internal)

- There may be a scientific dispute within the team during the course of the review
- SOPP 8006, Resolution of Differences in Scientific Judgment in the Review Process
  - Appeals are made up through the chain of command until resolution is reached
  - May be referred to a Center Coordinating Committee

ACTION
Not Ready for Approval

- **COMPLETE RESPONSE LETTER**
  - Itemizes all deficiencies in the application that must be corrected prior to approval
  - Stops the review clock
- **RESUBMISSION**
  - Class 1 or 2
  - Restarts the clock

PDUFA Resubmissions

- **Guidance for Industry: Classifying Resubmissions in Response to Action Letters, May 14, 1998**
- **SOPP 8405.1 Procedures for the Classification of Resubmissions of an Application for a Product Covered by PDUFA (5/20/98)**
- **Performance Goals**
  - **Class 1 resubmission 90% in 2 months**
  - **Class 2 resubmission 90% in 6 months**

External Dispute Resolution

- **Guidance for Industry: Formal Dispute Resolution: Appeals Above the Division Level**
- **SOPP 8005 Major Dispute Resolution Process**
  - **Disputes that cannot be resolved at the division level**
  - **Under PDUFA, timelines are provided, e.g., act on 90% within 30 days**

ACTION
Approval

- Compliance check
- Summary of Basis for Approval (SBA)
- Finding of No Significant Impact (FONSI) or confirm categorical exclusion
- Approval letter
  - Grants permission to distribute
  - Itemizes all agreements & commitments
- Issue license

Review Oversight

- **Routine review oversight**
  - Branch Chief
  - Division Director
  - Office/Center Director
- **Dispute Resolution**
  - Internal - SOPP 8006
  - External - SOPP 8005
- **Quality Assurance**
  - Clinical Hold Oversight Committee
  - Refusal to File Oversight Committee

First Level of Review Oversight

- **Branch/Lab Chief**
  - **Branch/Lab Chief concurrence/non-concurrence of a discipline reviewer's comments and recommendation**
  - **Based on**
    - **Current scientific knowledge base of the proposed product**
    - **Ongoing research in that product's area, I.e., peer reviewed journals, scientific meetings, CBER research, etc.**
  - **Factoring in**
    - **PHS and FD&C Acts as appropriate**
    - **Applicable regulations**
    - **Applicable guidances**
    - **Applicable CBER Standard Operating Procedures and Policies**

Second Level of Review Oversight

- **Division Director**
  - **Division Director concurrence/non-concurrence of all discipline reviews and recommendations from the review team and weighs an approval or deficiency action**
    - **Based on**
      - **Current scientific knowledge base of the proposed product**
      - **Ongoing research in that product's area, I.e., peer reviewed jou rnals, scientific meetings, CBER research, etc.**
    - **Factoring in**
      - **PHS and FD&C Acts as appropriate**
      - **Applicable regulations**
      - **Applicable guidances**
      - **Applicable CBER Standard Operating Based on**

Third Level of Review Oversight

(Usually for New or Unique Products)

- **Office/Center Director**
  - **Office/Center Director concurrence/non-concurrence of all discipline reviews and recommendations of the review team and weighs an approval or deficiency action recommended by the Division Director**
    - **Based on**
      - **Current scientific knowledge base of the proposed product**
      - **Ongoing research in that product's area, I.e., peer reviewed jou rnals, scientific meetings, CBER research, etc.**
    - **Factoring in**
      - **PHS and FD&C Acts as appropriate**
      - **Applicable regulations**
      - **Applicable guidances**
      - **Applicable CBER Standard Operating Based on**

CBER Management Oversight

- **SOPP for Major Dispute Resolution**
- **Clinical Hold Oversight**
- **Refusal to File Oversight**

CBER Management Oversight: QA

- **Clinical Hold Oversight Committee**
  - **Composed of representatives from**
    - **CBER Management (Review Management, Policy, QA, Deputy Director for Medicine and Center Director)**
    - **Product Offices (OBRR, OVRR, OTRR, OCBQ)**
    - **Center for Drugs (Office of Medical Products)**
  - **Review team presents a summary highlighting the reason for the Clinical Hold**
  - **IND/IDE Sponsor is invited to present their point of view**
  - **Evaluates the quality of the review process**

CBER Management Oversight: QA

- **Refuse to File Oversight Committee**
  - **Composed of representatives from**
    - **CBER Management (Review Management, Policy, QA, Deputy Director for Medicine, Center Director)**
    - **Product Offices (OBRR, OVRR, OTRR, OCBQ)**
    - **Center for Drugs (Office of Medical Products)**
  - **Review team presents a summary highlighting the reason for the refusal to file**
  - **The Applicant is invited to present their point of view**
  - **Evaluates the quality of the review process**

MANUAL OF STANDARD OPERATING PROCEDURES AND POLICIES

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http://www.cber.fda.gov/sopp/toc.htm